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Chronic Delta Hepatitis: Is the Prognosis Worse When Associated With Hepatitis C Virus and Human Immunodeficiency Virus Infections?

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Eighty-six patients were followed for 6.5 years to study the epidemiological, virological, and histological course of chronic delta hepatitis and the relationship of this disease with HIV and HCV infection.

Patients were classified into four groups according to simultaneous HCV and/or HIV infection: group 1, HDV infection (20 cases); group 2, HDV and HCV infection (11 cases); group 3, HDV and HIV infection (12 cases), and group 4, HDV, HCV, and HIV infection (43 cases). All but 14 patients were asymptomatic at presentation. Liver histology showed chronic active hepatitis in 53 cases and cirrhosis in 19 cases. During follow-up, 52 patients remained asymptomatic, 34 developed hepatic dysfunction, 28 died, and 1 received a liver transplant. Among the 28 patients who died, 4 had HDV infection; 3 HDV and HCV infection; 3 HDV and HIV infection; and 18 HDV, HCV, and HIV infection. Death was due to liver failure in 16 (57%), AIDS in 10 (36%), and was unrelated to liver disease in 2 (8%) cases. There results demonstrate that chronic delta hepatitis is a severe disease, especially among drug users with HIV and HCV infection. The high morbidity and mortality of chronic delta hepatitis justifies the use of antiviral therapy to modify the natural course of the disease.

KEY WORDS: epidemiology, virology, histology

INTRODUCTION

Hepatitis D virus (HDV) infection can occur either simultaneously with acute hepatitis B virus (HBV) infection (coinfection) or superimposed on chronic HBV infection (superinfection). In coinfection, the acute disease is usually self-limited, although a fulminant course may also occur. Superinfection by HDV on an HBsAg chronic carrier state is generally associated with severe liver disease, progressing to cirrhosis in 70–80% of patients [Rizzetto, 1983; Saracco et al., 1987].

Patients with both hepatitis D viremia and hepatitis B viremia have been identified as those with the most unfavorable outcome, suggesting that HBV replication modulates the course of chronic hepatitis D [Smedile et al., 1991]. Other factors that may modify the prognosis of chronic delta infection are coinfection with other viruses, such as hepatitis C virus (HCV) and/or human immunodeficiency virus (HIV) [Cassidy et al., 1989].

In our country, the majority of chronic delta hepatitis occurs in parenteral drug users, while it is rare in the general population, accounting for less than 5% of chronic hepatitis B cases.

The aim of this study was to assess the natural course of chronic delta hepatitis in our country. For this purpose, the clinical, serological and hitological course of this disease was monitored in a retrospective study of a cohort of affected patients. The relationship of chronic delta hepatitis with hepatitis B viremia and HCV- and/or HIV-associated infection, was also determined.

PATIENTS AND METHODS

Patients

Eighty-six patients with chronic hepatitis B and antibodies to HDV (anti-HD), referred to our department between 1978 and 1995, were studied. The diagnosis of chronic liver disease was established by elevated serum alanine transferase (ALT) levels for more than six months, and/or liver histology. The specific diagnosis of chronic delta infection was based on the presence of high levels of anti-HD and/or detection of delta antigen (HDAg) in the liver.

During the first visit, a clinical history that was especially thorough concerning epidemiological risk factors, a physical examination, and tests of biochemical and

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serological markers were performed. Patients were followed periodically and sampled every 6 months for an average of 6.5 years (range: 1 to 15 years).

A liver biopsy was undertaken in 71 patients at presentation. During follow-up, a second liver biopsy was carried out in 19 patients after a mean interval of 3.3 years (1–13 years). Liver specimens were fixed in formalin and embedded in paraffin for routine histological examination, and stained for HDAg by a peroxidase-antiperoxidase technique (anti-delta HRP, Sorin Biomedica, Italy).

The course of liver disease was studied by evaluating major clinical events, including the appearance of ascites, encephalopathy, bleeding, development of hepatocellular carcinoma, and death. None of the patients received antiviral therapy.

Serological and Virological Analysis

Serum was tested for hepatitis B surface antigen (HBsAg) and antibody to HCV (anti-HCV) by enzyme immunoassay (EIA) (Abbott, Auszyme monoclonal; and Abbott, HCV, respectively. Abbott Laboratories, North Chicago, IL). Hepatitis B e antigen (HBeAg), antibody to HBeAg (anti-HBe) and anti-HD were detected by commercial radioimmunoassay (Abbott-HBe; Antidelta; Abbott Laboratories, North Chicago, IL). Antibody to human immunodeficiency virus (anti-HIV) was determined by EIA (HIV-1/HIV-2 Abbott) and positive results were confirmed by Western blot.

Serum HBV-DNA and HDV-RNA were evaluated by dot-blot hybridization and PCR techniques as described previously [Buti et al., 1993; Jardi et al., 1995].

Fisher's exact test was used for statistical evaluation. A P value lower than 0.05 was considered significant.

RESULTS

Seventy-four (86%) of the 86 patients were male, and 12 (14%) were female; the median age was 24 years (range: 12–70 years). Sixty-six (77%) were parenteral drug abusers, 3 (3.4%) were hemophiliacs, 2 (2.3%) had sexual contact with HDV-infected subjects, and in 15 (17.3%) no risk factors were identified. At presentation, all patients had elevated ALT levels and were asymptomatic, except for 14 patients who had decompensated liver disease (ascites and/or jaundice). Fifty-four (62%) patients had HCV antibodies, and 53 (61%) had HIV antibodies.

Patients were classified into four groups according to their HCV and HIV status: group 1, HDV infection only (20 cases); group 2, HDV and HCV infection (11 cases); group 3, HDV and HIV infection (12 cases); and group 4, HDV, HCV, and HIV infection (43 cases). Parenteral risk factors were present in 45% of HDV infections; in 63% if HCV and HDV infections; in 83% of HDV and HIV infections; and in all cases of HDV, HCV, and HIV infection. Clinical, virological and histological characteristics are shown in Table I.

Hepatitis B Virus Replication

With respect to HBV replication in the 55 anti-HIV-positive cases, HBeAg was detected in 30 (54.5%), and HBV-DNA in 35 (63.6%) by dot-blot and 44 (80%) by PCR. On the other hand, of the 31 anti-HIV-negative cases, HBeAg was present in 8 (26%), HBV-DNA in 10 (32%) by dot-blot and in 18 (58%) by PCR. HDV-RNA was detected by dot-blot 31 (64%) and by PCR in 47 (85%) of the anti-HIV-positive cases, respectively, and in 18 (58%) and 25 (81%) of the anti-HIV-negative cases, respectively (p:ns).

During follow-up, HBeAg cleared in 24 (63%) out of 38 patients that were initially positive, after a mean time of 1.6 years (17 patients remained asymptomatic and 7 died). HBeAg remained detectable in 14 patients (2 died and 12 remained asymptomatic). HBsAg disappeared in 6 patients (3 of whom where initially HBeAg-positive): 4 were asymptomatic and 2 died; clearance of HBsAg occurred after a mean time of 5.2 years.

Histological Studies

Sequential histological study was carried out in 19 patients. In the first liver sample, chronic active hepatitis (CAH) was present in 14 cases and cirrhosis in 5 cases. Hepatic HDAg was detected in 14 cases. In the second liver biopsy, performed after a mean time of 3.3 years, CAH was present in 3 cases and cirrhosis in 16 cases. In summary, liver histology improved in two cases, did not change in 4 and worsened in 13. Histology improved only in the two patients in whom hepatic HDAg cleared.

Clinical Outcome

During a mean follow-up of 6.5 years, 52 (65%) of the patients remained asymptomatic and 34 (35%) experienced an episode of hepatic decompensation (jaundice, variceal bleeding, or ascites). Among the 34 decompensated patients, one received a liver transplant and is alive, 4 had ascites and 28 died.

The characteristics and type of infection of the 28 patients who died are in Tables I and II. None of the patients developed hepatocellular carcinoma. The anti-HIV-positive patients who died were more frequently young males who werre HBeAg, HBV-DNA, HDV-RNA and anti-HCV positive, while the anti-HIV-negative cases were older, had more severe liver disease and fewer histological and serological markers of viral replication. In the latter group, the majority of deaths were due to liver failure.

One patient underwent liver transplantation and experienced a reactivation of HBV. One year after liver transplantation, hepatic HBcAg was positive and HDAg remained undetectable.

DISCUSSION

Chronic delta hepatitis is a severe form of liver disease in which spontaneous resolution is rare. Long-term studies have shown that cirrhosis develops in 60–70% of patients and that the disease may be rapidly progressive, especially among IV drug addicts [Rizzetto et al., 1983; Govidarajan et al., 1986, Craxi et al., 1993]. About 15% of these patients develop cirrhosis within two years after the onset of acute hepatitis Saracco et al., 1987]. In this

TABLE I. Clinical, Virological, and Histological Characteristics of the 86 Patients Classified in Four Groups

	HDV	HDV + HCV	HDV + HIV	HDV + HCV + HIV
No Cases	20	11	12	43
Sex, male (%)	11 (55%)	9 (82%)	9 (75%)	41 (95%)
Age (yr)	29.76 ± 12.52	30.8 ± 14.8	23.58 ± 4.5	23.65 ± 4.3
HBeAg	4 (20%)*	4 (36%)	7 (64%)*	23 (53%)*
HBV-DNA + by dot blot	5 (25%)*	5 (45%)	9 (75%)*	26 (60%)*
HBV-DNA + by PCR	10 (50%)*	8 (73%)	10 (83%)*	34 (79%)*
HDV-RNA + by dot blot	11 (55%)	7 (64%)	8 (67%)	30 (70%)
HDV-RNA + by PCR	16 (80%)	9 (82%)	9 (75%)	38 (88%)
Liver Biopsy	17 Cases	10 Cases	6 Cases	39 Cases
CAH	11 (65%)	5 (50%)	4 (80%)	33 (86%)
Cirrhosis	6 (35%)	5 (50%)	2 (20%)	6 (14%)
Clinical outcome				
Death[a]	4 (20%)	3 (27%)	3 (25%)	18 (42%)*
Hepatic events[b]	1 (5%)	1 (9%)	2 (17%)	2 (5%)
Serological outcome				
HBsAg	1 (5%)	0	0	5 (12%)
HBeAg	1 (25%)	4 (100%)	0	17 (74%)

[a]Cause of death was liver failure in 16, AIDS in 10, and other reasons in 2 cases.
[b]Hepatic events were 2 episodes of variceal bleeding, 2 of ascites, and 2 of jaundice and ascites.
*$P < 0.05$.

TABLE II. Characteristics of 28 Patients With Chronic Delta Hepatitis Who Died, Classified According to Their HIV Status

	Anti-HIV+ (21 cases)	Anti-HIV− (7 cases)
Age (yr)	24.19 (17–34)	43.85 (18–70)
Sex, male	19 (90%)	3 (43%)
IV drug addiction	11 (52%)	0
Serological markers		
HBeAg+	9 (43%)	0
HBV-DNA+	20 (95%)*	2 (28.5%)*
HDV-RNA+	20 (95%)*	3 (43%)*
anti-HCV+	18 (86%)	3 (43%)
Histological Lesion		
CAH	12 (70.5%)	
Cirrhosis	5 (29.5%)	7
Cause of death		
Liver Failure	10 (48%)	6 (86%)
Non-Hepatic	11 (52%)	1 (14%)
Follow-up[a]	3.82 (3m-9y)	6.08 (6m-13y)

[a]m = month, y = year.
*$P < 0.05$.

study, the histological lesion worsened in 68% of patients during the first 3 years, despite the clearance of serum HBeAg and HBV-DNA, and intrahepatic HBcAg. The high rate of seroconversion to anti-HBe could be explained by the fact that the majority of these infections were acquired recently or, alternatively, by the inhibition of HBV replication by HDV infection, especially among HIV-negative subjects. However, this does not seem to be the case in HIV positive-patients in whom high levels of HDV and HBV replication have been described. Smedile et al. [Smedile et al., 1991], suggested that HBV replication can modulate and worsen hepatitis D infection while HBV-DNA negative chronic delta hepatitis has a better prognosis with fewer hepatic decompensation events. It is still unclear whether HIV infection influences chronic delta hepatitis: while in one study HIV did not seem to modify HBV or HDV infection [Housset et al., 1992], another report showed that HIV infection modified the course of HDV and HBV infection and resulted in a poorer prognosis [Monno et al., 1991]. In the present study, the majority of patients with hepatitis B and hepatitis D viremia were IV drug addicts with HIV and HCV infection. The anti-HIV-positive patients had a high rate of mortality and morbidity for hepatic and non-hepatic events, while the most benign outcome occurred in non-addicts, the majority of whom were HIV negative without markers of HBV replication, thus suggesting that a normal or near normal immune response improved the course of delta infection. HCV-associated infection, which is more frequent in HIV-positive patients, may also play a role in the most severe form of chronic delta infection. Some studies suggest that HCV is the most important hepatotropic virus involved in HBsAg clearance in chronic hepatitis D [Sheen et al.,

1994]. Surprisingly, in our study, disappearance of HBsAg was more frequent in patients who were both HIV- and HCV-positive than in those who were HCV-positive alone, suggesting that HIV infection can alter HBsAg synthesis, as described previously [Caredda et al., 1989], or alternatively, that HIV can enhance the clearance of HBsAg.

In the present study, the overall mortality was 47%, and the mortality in chronic HDV infection alone was 20%, higher than that observed in chronic HBV infection [Craxi et al., 1993]. The overall mortality was higher than that reported by Rizzetto et al. [1983] and Govindarajan et al. [1986] in their series (the mortality was 30% and 25%, respectively), demonstrating that hepatitis delta infection in young, male IV drug users has an aggressive and progressive course. Although the severity of liver damage was similar in drug users and non-drug users, disease progressed more rapidly in the former, a fact for which there is no explanation. The cause may reside in simultaneous HBV replication and HCV infection, which was more frequent among drug users. Moreover, and in contrast with non-addicts, cessation of hepatitis D viremia is infrequent among drug-users [Ackerman et al., 1992]. The high rate of mortality due to liver disease and the favorable response to interferon therapy in anti-HIV-positive patients, as demonstrated in another study [Buti et al., 1992], suggests that patients with chronic hepatitis D should be considered for antiviral therapy.

In summary, chronic delta infection has two different clinical spectra: one affecting young, male IV drug users coinfected with HCV and HIV, with a high rate of morbidity and mortality due to liver disease; another affecting older patients without apparent risk factors for parenteral infection, with a slower progression of disease. We consider that all patients with chronic delta hepatitis should be evaluated for interferon therapy irrespective of the HIV status.

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